CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040232

Trade Name : METHYLPREDNISOLONE TABLETS USP

Generic Name: Methylprednisolone Tablets USP 4mg

Sponsor : Chelsea Laboratories, Inc.

Approval Date: October 16, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040232

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EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040232

APPROVAL LETTER

ANDA 40-232

OCT 16 1997

Chelsea Laboratories, Inc.
Attention: Ernest Lengle, Ph.D.
P.O. Box 15686
8606 Reading Road
Cincinnati, OH 45215-0686

Dear Sir:

This is in reference to your abbreviated new drug application dated December 20, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Methylprednisolone Tablets USP, 4 mg.

Reference is also made to your amendments dated February 14, July 18, September 3, and September 9, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Methylprednisolone Tablets USP, 4 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Medrol® Tablets, 4 mg of Pharmacia and Upjohn Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ for 10/16/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040232

FINAL PRINTED LABELING

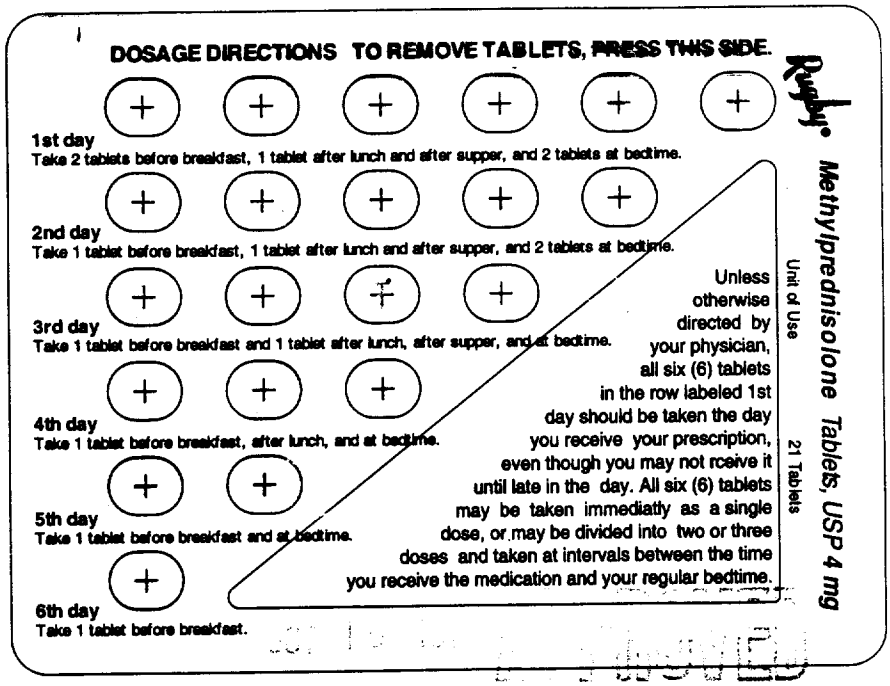
Chelsea Laboratories, Inc.

Methylprednisolone Tablets, USP 4 mg ANDA 40-232

Blister Pack Lidding
Commodity # 50013071

Please note that this is a proof of the final printed labeling for the blister pack lidding. This printing, which is a copy of the printer's acetate film, is as it will appear on the foil blister pack lidding. Final printed labeling on the foil blister pack lidding will be provided to the agency in the first annual report.

FRONT



BACK

Methylprednisolone *Tablets, USP 4 mg*

Unit of Use

21 Tablets

APPROVED

NDC 0536-4036-44
Prod. No. 004-0361

Rugby®

Methylprednisolone Tablets, USP
4 mg
Unit of Use-21 Tablets

Each tablet contains: Methylprednisolone, USP..... 4 mg

See package for full prescribing information.

Keep patient under close observation of a physician.

Store at controlled room temperature, 15°-30°C (59°-86°F)

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

MANUFACTURED FOR RUGBY LABORATORIES, INC.

NORCROSS, GEORGIA 30071

50013072

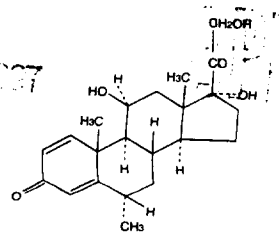
N 3 0536-4036-44 4

METHYLPREDNISOLONE TABLETS, USP

DESCRIPTION

Methylprednisolone Tablets, USP contain methylprednisolone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in dioxane, and in methanol, slightly soluble in acetone, and in chloroform, and very slightly soluble in ether. It is practically insoluble in water.

The chemical name for methylprednisolone is 11β,17,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione and the molecular weight is 374.48. The molecular formula is $C_{22}H_{30}O_5$. The structural formula is represented below:



APPROVED

Each Methylprednisolone tablet, for oral administration, contains 4 mg of methylprednisolone. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, anhydrous lactose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polacrilin potassium, sodium starch glycolate, and stearic acid.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli

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Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS AND USAGE

Methylprednisolone Tablets are indicated in the following conditions:

1. **Endocrine Disorders**
   - Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).
   - Congenital adrenal hyperplasia
   - Nonsuppurative thyroiditis
   - Hypercalcemia associated with cancer
2. **Rheumatic Disorders**
   - As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
   - Ankylosing spondylitis
   - Acute and subacute bursitis
   - Synovitis of osteoarthritis
   - Acute nonspecific tenosynovitis
   - Post-traumatic osteoarthritis
   - Psoriatic arthritis
   - Epicondylitis
   - Acute gouty arthritis
3. **Collagen Diseases**
   - During an exacerbation or as maintenance therapy in selected cases of:
   - Systemic lupus erythematosus
   - Systemic dermatomyositis (polymyositis)
   - Acute rheumatic carditis
4. **Dermatologic Diseases**
   - Bullous dermatitis herpetiformis
   - Severe erythema multiforme (Stevens-Johnson syndrome)
   - Severe seborrheic dermatitis
   - Exfoliative dermatitis
   - Mycosis fungoides
   - Pemphigus
   - Severe psoriasis
5. **Allergic States**
   - Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
   - Seasonal or perennial allergic rhinitis
   - Drug hypersensitivity reactions
   - Serum sickness
   - Contact dermatitis
   - Bronchial asthma
   - Atopic dermatitis
6. **Ophthalmic Diseases**
   - Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
   - Allergic corneal marginal ulcers
   - Herpes zoster ophthalmicus
   - Anterior segment inflammation
   - Diffuse posterior uveitis and choroiditis
   - Sympathetic ophthalmia
   - Keratitis
   - Optic neuritis
   - Allergic conjunctivitis
   - Chorioretinitis
   - Iritis and iridocyclitis
7. **Respiratory Diseases**
   - Symptomatic sarcoidosis
   - Berylliosis
   - Loeffler's syndrome not manageable by other means
   - Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
   - Aspiration pneumonitis
8. **Hematologic Disorders**
   - Idiopathic thrombocytopenic purpura in adults
   - Secondary thrombocytopenia in adults
   - Acquired (autoimmune) hemolytic anemia
   - Erythroblastopenia (RBC anemia)
   - Congenital (erythroid) hypoplastic anemia
9. **Neoplastic Diseases**
   - For palliative management of:
   - Leukemias and lymphomas in adults
   - Acute leukemia of childhood
10. **Edematous States**
    - To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.
11. **Gastrointestinal Diseases**
    - To tide the patient over a critical period of the disease in:
    - Ulcerative colitis
    - Regional enteritis
12. **Nervous System**
    - Acute exacerbations of multiple sclerosis
13. **Miscellaneous**
    - Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
    - Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

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Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of child-bearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restrictions and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of Methylprednisolone Tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General Precautions

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerabations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION.**)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Since concurrent use of these agents results in a mutual inhibition of metabolism, it is possible that adverse events associated with the individual use of either drug may be more apt to occur.

Information for the Patient

Persons who are on immunosupressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances
Sodium retention
Congestive heart failure in susceptible patients
Hypertension
Fluid retention
Potassium loss
Hypokalemic alkalosis
Musculoskeletal
Muscle weakness
Loss of muscle mass
Steroid myopathy
Osteoporosis
Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones
Gastrointestinal
Peptic ulcer with possible perforation and hemorrhage
Pancreatitis
Abdominal distention
Ulcerative esophagitis
Dermatologic
Impaired wound healing
Petechiae and ecchymoses
May suppress reactions to skin tests
Thin fragile skin
Facial erythema
Increased sweating
Neurological
Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment
Convulsions
Vertigo
Headache
Endocrine
Development of Cushingoid state
Suppression of growth in children
Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
Menstrual irregularities
Decreased carbohydrate tolerance
Manifestations of latent diabetes mellitus
Increased requirements for insulin or oral hypoglycemic agents in diabetics
Ophthalmic
Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma
Exophthalmos
Metabolic
Negative nitrogen balance due to protein catabolism
The following additional reactions have been reported following oral as well as parenteral therapy:
Urticaria and other allergic, anaphylactic or hypersensitivity reactions.

DOSAGE AND ADMINISTRATION

The initial dosage Methylprednisolone Tablets may vary from 4 mg to 48 mg of methylprednisolone per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, Methylprednisolone Tablets should be discontinued and the patient transferred to other appropriate therapy.

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of Methylprednisolone Tablets for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

Multiple Sclerosis

In treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

Alternate day therapy

Alternate day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (a) the anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects and (b) administration of the corticosteroid every other morning allows for reestablishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-steroid day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increased corticotropin (ACTH) with

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A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 pm to a peak level about 6 am. Increasing levels of ACTH stimulate adrenal cortical activity resulting in a rise in plasma cortisol with maximum levels occurring between 2 am and 8 am. This rise in cortisol dampens ACTH production and in turn adrenal cortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenal cortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term pharmacologic dose corticoid therapy administered in conventional daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every six hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used.

Further, it has been shown that a single dose of certain corticosteroids will produce adrenal cortical suppression for two or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenal cortical suppression for $1\frac{1}{4}$ to $1\frac{1}{2}$ days following a single dose) and thus are recommended for alternate day therapy.

The following should be kept in mind when considering alternate day therapy:

1) Basic principles and indications for corticosteroid therapy should apply. The benefits of alternate day therapy should not encourage the indiscriminate use of steroids.
2) Alternate day therapy is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticoid therapy is anticipated.
3) In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with alternate day therapy. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually four to ten days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternative day therapy is intended.

   Once control has been established, two courses are available: (a) change to alternate day therapy and then gradually reduce the amount of corticoid given every other day or (b) following control of the disease process reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (a) may be preferable.
4) Because of the advantages of alternate day therapy, it may be desirable to try patients on this form of therapy who have been on daily corticoids for long periods of time (e.g., patients with rheumatoid arthritis). Since these patients may already have a suppressed HPA axis, establishing them on alternate day therapy may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.
5) As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (e.g., dexamethasone and betamethasone).
6) The maximal activity of the adrenal cortex is between 2 am and 8 am, and it is minimal between 4 pm and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (am).
7) In using alternate day therapy it is important, as in all therapeutic situations to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of alternate day therapy will help the patient understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.
8) In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established alternate day therapy may be reinstituted.
9) Although many of the undesirable features of corticosteroid therapy can be minimized by alternate day therapy, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticoid therapy is being considered.

HOW SUPPLIED

Methylprednisolone Tablets, USP, 4 mg are white to off-white, oval debossed "Rugby and 4016" on one side and quadrisected on the other side and available in:

Bottles of 100 (NDC 0536-4036-01).

Unit of Use Blister Pack (21 tablets) (NDC 0536-4036-44).

Store at Controlled Room Temperature 15° to 30° C (59° to 86° F).

Dispense in a tight, light-resistant container as defined in USP/NF.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
Chelsea Laboratories, Inc.
Cincinnati, OH 45215

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METHYLPREDNISOLONE TABLETS, USP

DESCRIPTION

Methylprednisolone Tablets, USP contain methylprednisolone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in dioxane, and in methanol, slightly soluble in acetone, and in chloroform, and very slightly soluble in ether. It is practically insoluble in water.

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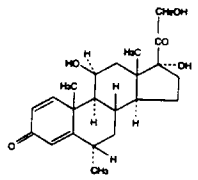

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INDICATIONS AND USAGE

Methylprednisolone Tablets are indicated in the following conditions:

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).

Congenital adrenal hyperplasia

Nonsuppurative thyroiditis

Hypercalcemia associated with cancer

2. Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)

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- Severe psoriasis

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Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:

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Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:

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- Secondary thrombocytopenia in adults
- Acquired (autoimmune) hemolytic anemia
- Erythroblastopenia (RBC anemia)
- Congenital (erythroid) hypoplastic anemia

9. Neoplastic Diseases

For palliative management of:

- Leukemias and lymphomas in adults
- Acute leukemia of childhood

10. Edematous States

To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

11. Gastrointestinal Diseases

To tide the patient over a critical period of the disease in:

- Ulcerative colitis
- Regional enteritis

12. Nervous System

9. Neoplastic Diseases

For palliative management of:

Leukemias and lymphomas in adults

Acute leukemia of childhood

10. Edematous States

To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

11. Gastrointestinal Diseases

To tide the patient over a critical period of the disease in:

Ulcerative colitis

Regional enteritis

12. Nervous System

Acute exacerbations of multiple sclerosis

13. Miscellaneous

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of child-bearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restrictions and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of Methylprednisolone Tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG)

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PRECAUTIONS

General Precautions

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerabations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Since con-

5

(and ZOSTER immune globulin [VZIG]) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered.

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Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Since concurrent use of these agents results in a mutual inhibition of metabolism, it is possible that adverse events associated with the individual use of either drug may be more apt to occur.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances

Sodium retention

Congestive heart failure in susceptible patients

Hypertension

Fluid retention

Potassium loss

Hypokalemic alkalosis

Musculoskeletal

Muscle weakness

Loss of muscle mass

Steroid myopathy

Osteoporosis

Vertebral compression fractures

Aseptic necrosis of femoral and humeral heads

Pathologic fracture of long bones

Gastrointestinal

Peptic ulcer with possible perforation and hemorrhage

Pancreatitis

Abdominal distention

Ulcerative esophagitis

Dermatologic

Impaired wound healing

Petechiae and ecchymoses

May suppress reactions to skin tests

Thin fragile skin

Facial erythema

Increased sweating

Neurological

Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment

Convulsions

Vertigo

Headache

Endocrine

Development of Cushingoid state

Suppression of growth in children

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness

Menstrual irregularities

Decreased carbohydrate tolerance

Manifestations of latent diabetes mellitus

Increased requirements for insulin or oral hypoglycemic agents in diabetics

Ophthalmic

Posterior subcapsular cataracts

Increased intraocular pressure

Glaucoma

Exophthalmos

Metabolic

Negative nitrogen balance due to protein catabolism

The following additional reactions have been reported following oral as well as parenteral therapy:

Urticaria and other allergic, anaphylactic or hypersensitivity reactions.

DOSAGE AND ADMINISTRATION

The initial dosage Methylprednisolone Tablets may vary from 4 mg to 48 mg of methylprednisolone per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, Methylprednisolone Tablets should be discontinued and the patient transferred to other appropriate therapy.

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of Methylprednisolone Tablets for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

Multiple Sclerosis

In treatment of acute exacerbations of multiple sclerosis daily doses of

be withdrawn gradually rather than abruptly.

Multiple Sclerosis

In treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

Alternate day therapy

Alternate day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (a) the anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects and (b) administration of the corticosteroid every other morning allows for reestablishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-steroid day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 pm to a peak level about 6 am. Increasing levels of ACTH stimulate adrenal cortical activity resulting in a rise in plasma cortisol with maximum levels occurring between 2 am and 8 am. This rise in cortisol dampens ACTH production and in turn adrenal cortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenal cortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term pharmacologic dose corticoid therapy administered in conventional daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every six hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used.

Further, it has been shown that a single dose of certain corticosteroids will produce adrenal cortical suppression for two or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenal cortical suppression for 1¼ to 1½ days following a single dose) and thus are recommended for alternate day therapy.

The following should be kept in mind when considering alternate day therapy:

1) Basic principles and indications for corticosteroid therapy should apply. The benefits of alternate day therapy should not encourage the indiscriminate use of steroids.

2) Alternate day therapy is a therapeutic technique primarily designed for patients in whom

Prednisone, a hydrocortisone prednisone and prednisolone are considered to be short acting (producing adrenal cortical suppression for 1¼ to 1½ days following a single dose) and thus are recommended for alternate day therapy.

The following should be kept in mind when considering alternate day therapy:

1) Basic principles and indications for corticosteroid therapy should apply. The benefits of alternate day therapy should not encourage the indiscriminate use of steroids.

2) Alternate day therapy is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticoid therapy is anticipated.

3) In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with alternate day therapy. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually four to ten days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternative day therapy is intended.

Once control has been established, two courses are available: (a) change to alternate day therapy and then gradually reduce the amount of corticoid given every other day or (b) following control of the disease process reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (a) may be preferable.

4) Because of the advantages of alternate day therapy, it may be desirable to try patients on this form of therapy who have been on daily corticoids for long periods of time (e.g., patients with rheumatoid arthritis). Since these patients may already have a suppressed HPA axis, establishing them on alternate day therapy may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.

5) As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (e.g., dexamethasone and betamethasone).

6) The maximal activity of the adrenal cortex is between 2 am and 8 am, and it is minimal between 4 pm and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (am).

7) In using alternate day therapy it is important, as in all therapeutic situations to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of alternate day therapy will help the patient understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.

8) In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established alternate day therapy may be reinstituted.

9) Although many of the undesirable features of corticosteroid therapy can be minimized by alternate day therapy, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticoid therapy is being considered.

HOW SUPPLIED

Methylprednisolone Tablets, USP 4 mg are white to off-white ...

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HOW SUPPLIED

Methylprednisolone Tablets, USP, 4 mg are white to off-white, oval debossed "Rugby and 4016" on one side and quadrisected on the other side and available in:

Bottles of 100 (NDC 0536-4036-01).

Unit of Use Blister Pack (21 tablets) (NDC 0536-4036-44).

Store at Controlled Room Temperature 15° to 30° C (59° to 86° F).

Dispense in a tight, light-resistant container as defined in USP/NF

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
Chelsea Laboratories, Inc.
Cincinnati, OH 45215

Rev. 4/97

50013070

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances

Sodium retention

Congestive heart failure in susceptible patients

Hypertension

Fluid retention

Potassium loss

Hypokalemic alkalosis

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040232

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-232

3. NAME AND ADDRESS OF APPLICANT
Chelsea Laboratories, Inc.
Attention: Ernest Lengle, Ph.D.
P.O. Box 15686
8606 Reading road
Cincinnati, OH 45215-0686

4. LEGAL BASIS FOR SUBMISSION
Approved Application for Medrol®; (The Upjohn Company)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Methylprednisolone, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original Application Submission Date December 20, 1996
Amendment Date April 11, 1997 (firm submitted additional proposed packaging configuration; corrected two errors on the pre-approval stability protocol; included system suitability data).
Minor Amendment Date July 18, 1997 (This review).
Telephone Amendment Date September 3, 1997 (This Review).
Telephone Amendment Date September 9, 1997 (This Review).

10. PHARMACOLOGICAL CATEGORY
Synthetic Glucocorticoid, Primary Use as an Antiinflammatory Agent in Disorders of Many Organ Systems.

11. Rx or OTC
Rx

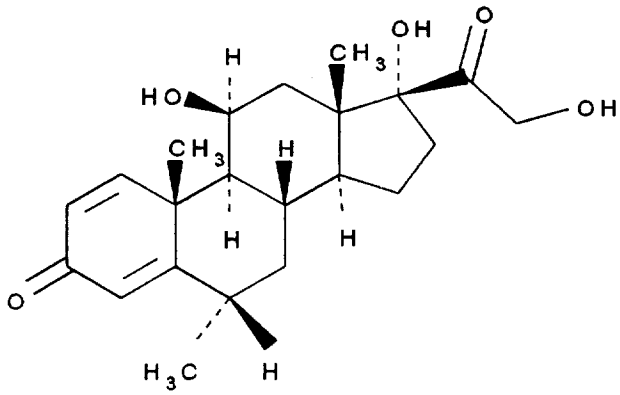
12. RELATED IND/NDA/DMF(s)
See DMF Section

13. DOSAGE FORM
Uncoated Tablet

14. POTENCY
4 mg

15. CHEMICAL NAME AND STRUCTURE

Methylprednisolone USP
$C_{22}H_{30}O_5$; M.W. = 374.48



11β,17,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione.
CAS [83-43-2]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
See Individual Review Sections; comments from deficiency letter are followed by firm's response. Also, see the Addendum to this review.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER:
U. S. Atwal

DATE COMPLETED:
August 8, 1997

Date Revised:
September 9, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040232

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #40232 **SPONSOR : Chelsea Laboratories**
DRUG & DOSAGE FORM : Methylprednisolone Tablet
STRENGTH (s) : 4 mg
TYPE OF STUDY: SD X SDF MULT OTHER
STUDY SITE: CLINICAL (b)4 - **ANALYTICAL :** (b)4 - Confidential

STUDY SUMMARY :

LSMEANS AND 90% CONFIDENCE INTERVALS

Parameter	Test Mean	Ref Mean	Ratio	Low CI	Upp CI
AUCI	526.11	521.23	1.01	97.13	104.75
AUCT	512.54	507.83	1.01	97.01	104.84
CMAX	110.55	115.33	0.96	92.26	99.46
LAUCI	509.70	507.02	1.01	97.05	104.13
LAUCT	496.11	493.51	1.01	96.97	104.22
LCMAX	108.84	112.84	0.96	93.03	100.00

DISSOLUTION : Apparatus: II, Paddle RPM: 50
Conditions: 900 mL Water

Dissolution Data Accepatable

PRIMARY REVIEWER : Jahnavi S. Kharidia **BRANCH : 3**
INITIAL : (b)4 - Confidential **DATE :** 8/26/97

BRANCH CHIEF : Ramakant M. Mhatre **BRANCH : 3**
INITIAL : (b)4 - Confidential **DATE :** 8/26/97

fw
DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL : (b)4 - Confidential **DATE :** 10/14/97

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL : _____ **DATE :**

JUN 10 1997

Methylprednisolone Tablets
4 mg
ANDA # 40-232
Reviewer: Jahnavi S. Kharidia
x:\wpfile\Biofinal\40232sd.597

Chelsea Laboratories, Inc.
8606 Reading Road
P.O. Box 15686
Cincinnati, Ohio 45215-0686
Submission Date: February 10, 1997

Review of a Bioequivalence Study and Dissolution Data

The firm has submitted a single-dose bioequivalence study under fasting conditions and dissolution data comparing its Methylprednisolone tablet, 4 mg with The Upjohn Company's Medrol®, 4 mg tablet. The application contains an electronic submission file for the bioequivalence study data.

Introduction

Methylprednisolone is a synthetic glucocorticoid, used primarily as antiinflammatory or immunosuppressant agent. It is indicated in endocrine and rheumatic disorders, collagen and dermatological diseases, allergic states, ophthalmic and respiratory diseases, hematological disorders, neoplastic diseases, edematous states, gastrointestinal diseases and multiple sclerosis, tuberculosis, meningitis and trichinosis. It is readily absorbed from gastrointestinal tract with peak plasma levels occurring at 1-2 hours. The plasma half-life is about 3-4 hours.

The reference listed drug is Medrol® manufactured by The Upjohn Company. It is available in six strengths: 2 mg, 4 mg, 8 mg, 16 mg, 24 mg, and 32 mg.

Objective

The objective of this study was to compare the bioavailability of Chelsea's Methylprednisolone tablets, 4 mg, to that of a reference listed drug, Medrol® tablets, 4 mg, manufactured by The Upjohn Company.

Fasting Study

1. Protocol Number:

   #P96-280: A Relative Bioavailability Study of Methylprednisolone 4 mg Tablets Under Fasting Conditions

2. Study Sites and Investigators:

(b)4 - Confidential Business

3. Study Design:

This study was a randomized, single-dose, two-way crossover design involving twenty-six healthy male subjects.

4. Subject Inclusion/Exclusion Criteria:

Twenty six healthy male subjects were enrolled in the study.

Inclusion Criteria:

Subjects meeting the following criteria were included in the study.

a) Male, healthy, 18-50 years of age

b) Body weight of the subjects within ± 10% of the ideal weight

c) Normal findings in the physical examination, vital signs and ECG

d) Blood chemistry, hematology and urine analysis values within clinically acceptable limits

Exclusion Criteria:

Subjects meeting the following criteria were excluded from the study.

a) Known allergy to methylprednisolone or to other glucocorticoids

b) History of drug or alcohol addiction or abuse

c) Positive HIV 1, hepatitis B surface antigen screen or a reactive HIV 1 and 2 antibody screen

d) Any clinically significant illness during the 4 weeks prior to Period I dosing

e) Donation of greater than 150 mL of blood within 30 days prior to Period I dosing

5. Drug Treatments:

A. Test Product

Methylprednisolone Tablets, 4 mg
Mfg. Chelsea Laboratories, Inc.
Lot Number: 73000543R
Batch Size: (b)4 -Tablets

B. Reference Product

Medrol® Tablets,
Mfg: The Upjohn Company
Lot Number: 797KH
Exp. Date: 7/98

6. Dosing:

4 x 4 mg of Methylprednisolone Tablets

After an overnight fast of ten hours, each subject randomly received either a test product or a reference product with 240 mL of water. Standard meals were provided at 5 and 10 hours after dosing. Water was not permitted for 2 hours before and 2 hours after dosing in each period.

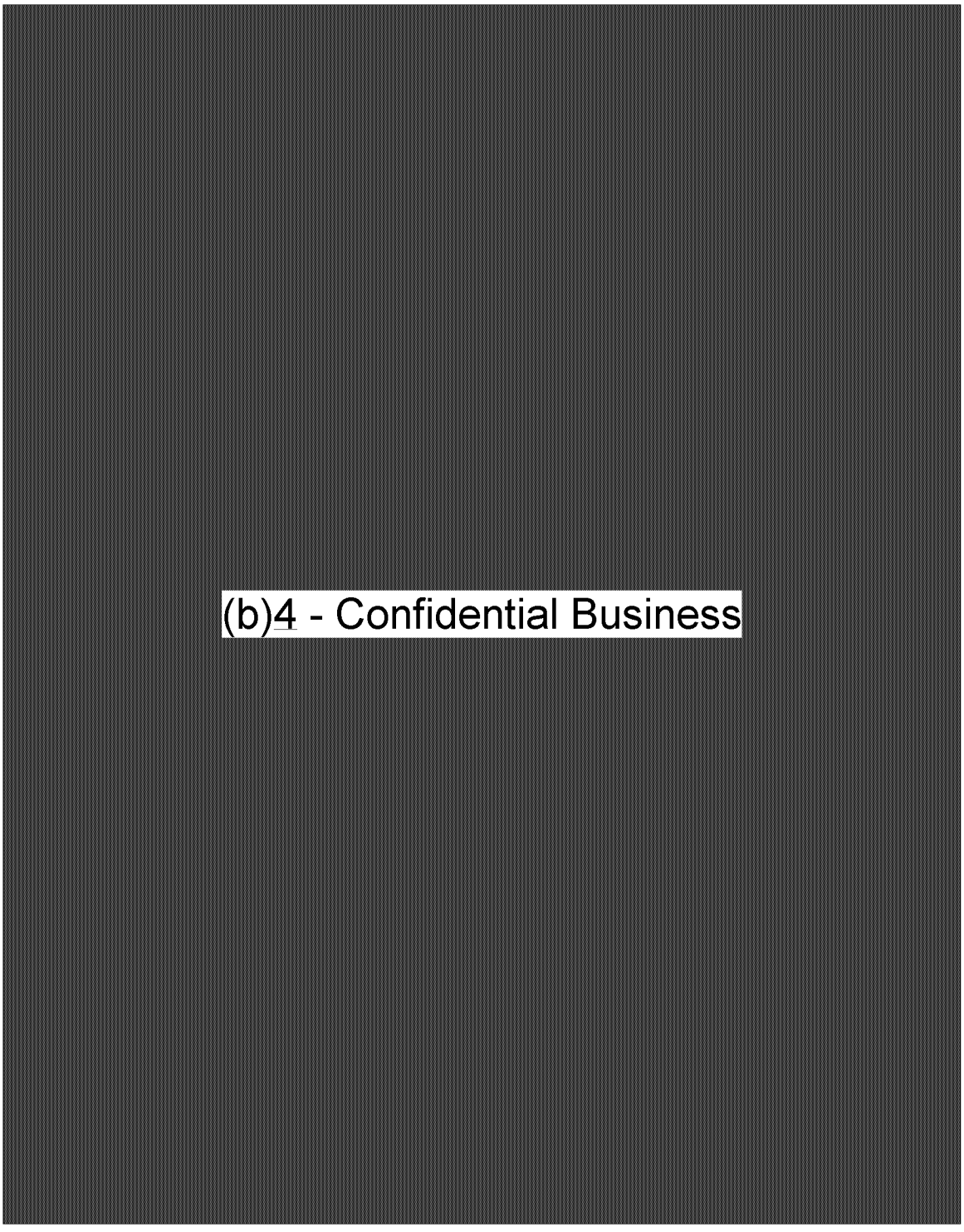
7. Housing:

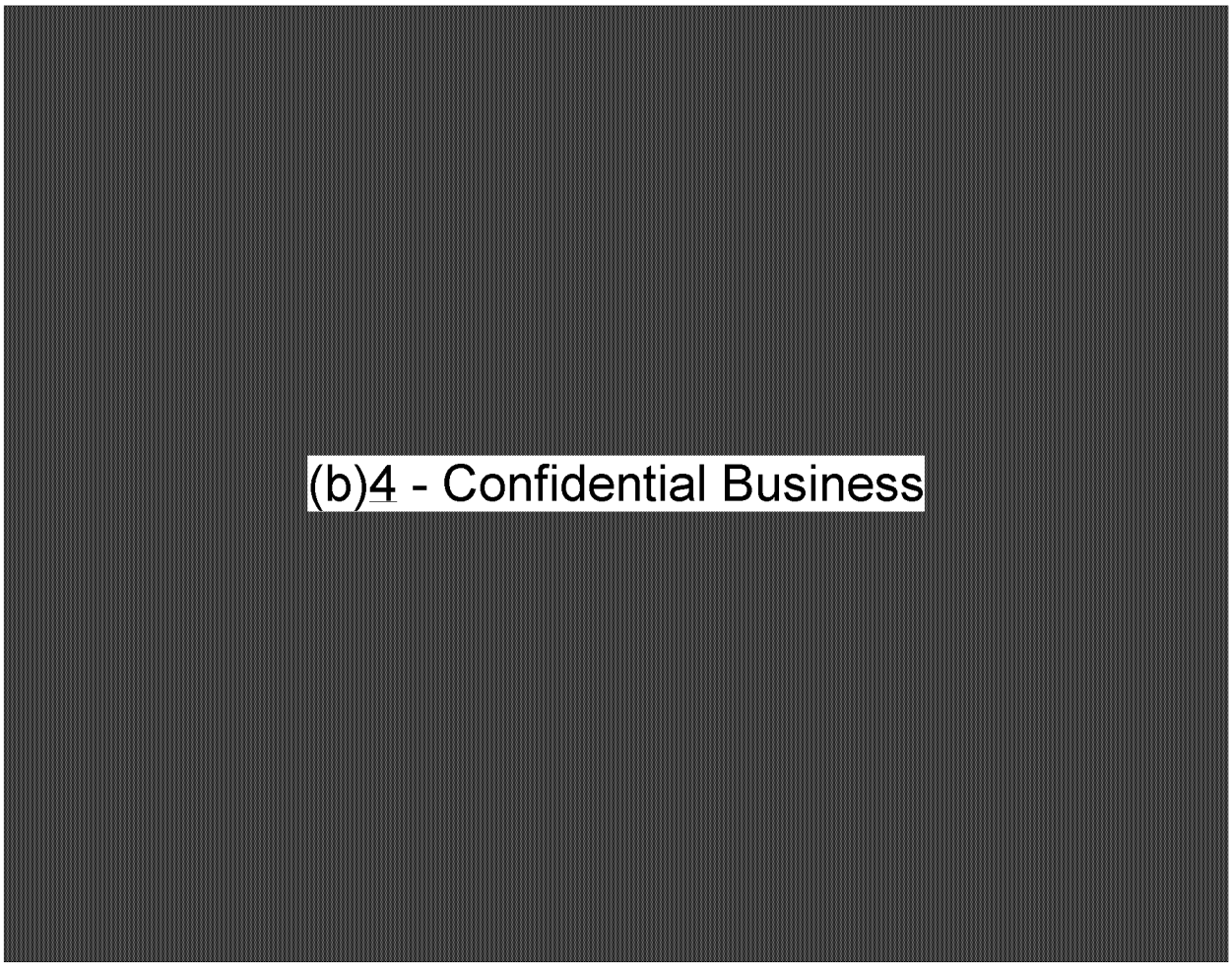
The subjects were housed in the facility from at least 10 hours before until at least 18 hours after drug administration. Subjects were not permitted to smoke from 1 hour prior to until 4 hours after dosing.

8. Blood Sampling:

A total of 17 blood samples (1X 10 mL each) were collected from each subject at 0 and at 20 minutes, 40 minutes, 60 minutes and at 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 18 hours after drug administration in each period. The blood samples were centrifuged and plasma samples were separated and stored at -20° C until analyzed.

Analytical Method





Results

Twenty-six (26) subjects were accepted in the study. Subject #18 dropped prior to Period II dosing secondary to a rash which required prescription medication. Twenty-five (25) subjects successfully completed the clinical portion of the study. The plasma samples from 25 subjects were assayed for methylprednisolone.

1. Adverse Events

Seventeen adverse events such as headache, arthralgia, myalgia, pharyngitis, rhinitis and vomiting were reported in ten of twenty-six subjects. None of the adverse events were considered serious.

2. Deviations in the study:

There were five protocol deviations from the protocol instructions. The deviations were as follows:

Subject No.	Medication	Daily Dose	Problem	Study Days
25	Clindamycin 1% Topical Solution	1App	Facial Acne	-1
10	Ibuprofen 200 mg	2tabs	Headache	-1
12	Multivitamins	1 tab	Health supplement	-6
25	Pseudoephedrine sulfate 120 mg, Dexbrompheniramine Maleate 6 mg	1 tab	Nasal Congestion	-7
26	Ibuprofen 200 mg	2 tabs	Headache	-3

- indicates prior to dosing period I

Based on available pharmacokinetic parameters, the medications should have been completely eliminated from the body prior to Period I dosing. Therefore, in the opinion of the clinical investigators, the reported medications should not affect study integrity, and subject enrollment was allowed.

3. Pharmacokinetics/Statistical Analysis

Mean Plasma Concentrations

Mean methylprednisolone plasma levels for both the test and reference formulations were comparable as shown in Table 2 and Figure 1.

Table 2: Mean methylprednisolone plasma levels for test and reference products

Time (hour)	Test (ng/mL) Lot # 73000543R		Reference (ng/mL) Lot # 797KH		Ratio T/R
	Mean	Std Dev	Mean	Std Dev	
0	0.00	0.00	0.00	0.00	.
0.33	6.45	8.30	8.60	9.33	0.75
0.67	40.45	8.13	41.78	33.14	0.97
1	68.49	30.93	69.83	36.55	0.98
1.5	94.66	30.09	95.65	29.39	0.99
2	100.74	20.71	105.86	26.09	0.95
2.5	101.49	18.10	105.04	21.38	0.97
3	92.04	18.14	93.02	19.53	0.99
4	73.76	20.48	71.86	15.07	1.03
5	56.58	22.17	54.22	14.15	1.04
6	38.67	17.38	36.69	10.32	1.05
8	18.78	10.80	17.37	6.47	1.08
10	8.92	5.90	8.53	4.03	1.05
12	4.51	3.88	3.56	2.97	1.27
14	1.33	2.53	1.21	1.85	1.09
16	0.50	1.43	0.17	0.83	3.05
18	0.28	0.98	0.14	0.68	2.09

Pharmacokinetic Parameters/Statistical Analysis

Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean reported pharmacokinetic parameters for methylprednisolone are shown in Table 3. There was no significant difference between the formulations for AUCI, LNAUCI, C_{max}, LNC_{max} and T_{max}. The differences between the LSMEAN of test formulation and the corresponding LSMEAN of reference formulation are 1% for AUCT, 1% for AUCINF and 4% for CMAX. The 90% confidence intervals about the ratio of the test mean to reference mean are within 80% to 120% for all the pharmacokinetic parameters (Table 4).

Table 3: Test mean/Reference mean ratios of methylprednisolone pharmacokinetic parameters

Parameter	Test Mean	SD	Ref Mean	SD	Ratio
AUCI	527.60	142.00	520.72	125.41	1.01
AUCT	514.00	140.60	507.32	124.25	1.01
CMAX	110.69	19.90	115.19	24.82	0.96
KE	0.36	0.08	0.36	0.07	0.98
LAUCI	511.09	0.25	506.44	0.24	1.01
LAUCT	497.48	0.26	492.94	0.25	1.01
LCMAX	108.99	0.18	112.71	0.21	0.97
THALF	2.10	0.82	2.06	0.90	1.02
TMAX	2.24	0.82	1.95	0.58	1.15

Table 4: LSMeans and 90% Confidence Intervals for methylprednisolone

Parameter	Test Mean	Ref Mean	Ratio	Low CI	Upp CI
AUCI	526.11	521.23	1.01	97.13	104.75
AUCT	512.54	507.83	1.01	97.01	104.84
CMAX	110.55	115.33	0.96	92.26	99.46
LAUCI	509.70	507.02	1.01	97.05	104.13
LAUCT	496.11	493.51	1.01	96.97	104.22
LCMAX	108.84	112.84	0.96	93.03	100.00

In Vitro Dissolution Testing

The firm has submitted dissolution data on its methylprednisolone tablet, 10 mg compared to the reference product Medrol® tablet, 4 mg. The drug products used in the dissolution tests were from the same batch used in the *in vivo* bioequivalence studies. The method and results are presented in Table 5.

Table 5

ANALYTE:	METHYLPREDNISOLONE
STRENGTH AND UNIT:	4 MG
DISSOLUTION METHOD:	USP XXIII
DISSOLUTION MEDIUM:	WATER
VOLUME:	900 ML
DISSOLUTION APPARATUS:	METHOD 2 (PADDLES)
RPM:	50
ASSAY METHOD:	(b)4 - Confidential
DISSOLUTION SPECIFICATION:	

Time(minutes)	Test (Lot # 73000543R)			Reference (Lot 797KH)		
	Mean	Range	CV%	Mean	Range	CV%
10.00	97.54	(b)4 - Confidential Business	1.48	80.55	(b)4 - Confidential Business	8.85
20.00	102.36		1.36	98.58		3.35
30.00	102.79		1.64	101.70		2.03
45.00	103.08		1.54	102.27		3.03

NOT TO BE RELEASED UNDER FOI - TABLE 6

Table 6: Compositions of Methylprednisolone Tablets

Ingredient	*Quantity (mg)*
Lactose Monohydrate, NF	(b)4 - 4
Anhydrous Lactose	
Cellulose, Microcrystalline NF	
Methylprednisolone	
Sodium Starch Glycolate, NF	(b)4 - fide
Croscarmellose Sodium, NF	
Polacrilin Potassium, NF	
Stearic Acid, NF	
Magnesium Stearate	

Comments:

1. Assay method validation: Pre-study and within-study validations are acceptable.

2. The mean plasma profiles of methylprednisolone for the test and reference products are comparable.

3. The test/reference ratios were within 0.97-1.05 range for the non-transformed and log-transformed AUCT, AUCI and C_{max}. The 90% confidence intervals for log-transformed AUCT, AUCI and C_{max} are all within 80-125% range.

4. There was no severe medical event which required a clinical action.

5. The size of the bio-batch wa(b)4 - tablets.

6. Test product met dissolution specifications published in USP XXIII. Dissolution data are acceptable.

Deficiency

None.

Recommendations:

1. The single-dose bioequivalence study under fasting conditions conducted by Chelsea Laboratories, on its Methylprednisolone 4 mg Tablet, lot #73000543R, comparing it to Medrol® 4 mg Tablet, manufactured by The Upjohn Company, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Chelsea's Methylprednisolone Tablet, 4 mg is bioequivalent to the reference product, Medrol® Tablet, 4 mg, manufactured by The Upjohn Company.

2. The dissolution testing conducted by the firm on its Methyprednisolone Tablets 4 mg, lot #73000543R, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   NL (b)4 of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm met the *in vivo* bioequivalence study and *in vitro* dissolution testing requirements and the application is approvable.

The firm should be informed of the above recommendations.

(b)4 -
Jahnavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE (b)4 -
FT INITIALED RMHATRE Date 5/21/97
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur: (b)4 - Date 6/10/1997
Confidential
Nicholas Fleischer, Ph.D.
for Director
Division of Bioequivalence

cc: ANDA # 40232 (original, duplicate), Kharidia, HFD-658HFD-630, Drug File, Division File